Eur J Cancer, Vol. 26, No. 1, pp. 71–72, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

Letter to the Editor

Severe Toxicity with Cytorhodin S

GEOFFREY FALKSON, HENDRÉ C. FALKSON and ALBERT S. ALBERTS

CYTORHODIN S-GLUCONATE (Rodorubicin) is a tetraglycosidic anthracycline with a high degree of cytotoxicity against tumor cell lines and a lack of cross resistance to doxorubicin. Preclinical toxicology showed nephrotoxicity, marginal bone marrow toxicity and reversible cardiotoxicity [1]. Further Phase I studies suggested that onset of proteinuria can be delayed by prolonging infusion time and increasing the infused volume [2].

We undertook a Phase II study to investigate the activity of cytorhodin S in patients with colorectal cancer.

Patients with histologically proven, advanced, measurable colorectal cancer were entered on the study. Eligibility criteria included a good performance status (PS), and normal hemogram, creatinine clearance, electrocardiogram and left ventricular ejection fraction (LVEF). After seven patients were entered on the study it was closed because of significant toxicity. The median age was 55; none had received prior radiotherapy and only one had had previous chemotherapy; three were male and four female; two were asymptomatic and five had a PS of 1. Sites of metastases were lung (2), peritoneum (1), liver (6), intraabdominal nodes (4) and distant nodes (4). Patients received cytorhodin S 1290 μg/m^2 as a 30 min infusion in 5% dextrose (as recommended by Behringwerke) every 3 weeks. One patient received four cycles, four received two cycles and two received only one cycle.

No therapeutic benefit was observed in any of the seven patients. Only mild nausea and vomiting, and no alopecia or hematologic toxicity occurred. However, all patients who received more than one cycle developed albuminuria, two patients developed hematuria, and five patients developed a decreased LVEF. The median onstudy LVEF was 60%; this fell to a median of 45% after one cycle of cytorhodin. In one patient, a 17-year-old female, heart failure was confirmed to be the cause of death. The LVEF was 52.9% at start of treatment, after the first cycle it was 48%, 53% after the 2nd cycle and 19.8% after the 3rd cycle. Treatment was stopped; two subsequent values, 15.3% and 14.5%, were measured before death. *Post mortem* examination showed a dilated heart with organized thrombi in the ventricles. Electron microscopy showed swelling and distortion and fragmentation of the cristae of mitochondria of the myocardial fibres.

Venous thrombosis at the site of infusion occurred without exception following all infusions of cytorhodin S. In two patients pulmonary embolism was considered to be the cause of death. In one of these patients, diffuse pulmonary emboli were found at *post mortem*; this patient had received only one dose of cytorhodin S 3 weeks before death.

Cardiotoxicity was more severe than expected with this 3-weekly dosage schedule and fatal cardiotoxicity was documented in one patient. Significant toxicity, combined with the finding that none of the seven patients treated with cytorhodin S had any improvement in their tumor status, made it mandatory to stop this study early. Despite excellent preclinical activity and the absence of hemopoietic toxicity further clinical trials of cytorhodin S do not seem warranted.

Accepted 26 September 1989.
Address for correspondence: Geoffrey Falkson M.D., Department of Medical Oncology, Private Bag X 169, Pretoria 0001, Republic of South Africa.
Supported in part by a grant from the National Cancer Association of South Africa.
Cytorhodin S supplied by Behringwerke AG, Marburg, F.R.G.

REFERENCES

1. Kraemer HP, Berscheid HG, Ronneberger H, Zilg H, Sedlacek HH. Preclinical evaluation of cytorhodin S, a new anthracycline with activity in a human tumor based screening system. 5th NCI–EORTC Symposium on New Drugs in Cancer Therapy, Amsterdam, 1986. Abstract No. 9:18.
2. Verweij J, van der Burg MEL, van Putten WLJ, Kraemer HP, Weidmann E, Stoter G. A phase I study of cytorhodin S. Proceedings 4th European Conference on Clinical Oncology and Cancer Nursing, Madrid, 1987. Abstract No. 324:86.